The Role of Platelet-Rich Plasma in Inducing Musculoskeletal Tissue Healing

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Abstract *Background* Platelet-rich plasma [PRP] has received increasing interest across many musculoskeletal disciplines and has been widely applied clinically to stimulate tissue healing in numerous anatomical regions. The known actions of platelet-derived factors suggest that PRP may have significant potential in the treatment of pathological conditions of cartilage, tendon, ligament, and muscle. *Purpose* The aim of this manuscript is to review current literature regarding the biology of PRP and the efficacy of using PRP to augment healing of tendon ligament and muscle injuries, as well as early osteoarthritis. *Methods* A comprehensive literature review of musculoskeletal applications of PRP was performed, including basic science and clinical studies such as randomized controlled trials, case controlled series, and case series. *Results* The most compelling evidence to support the efficacy of PRP is for its application to tendon damage associated with lateral and medial epicondylitis. Although some promising studies have been reported supporting the use of PRP in osteoarthritis and ligament and muscle injuries, it currently remains unknown whether PRP effectively alters the progression of osteoarthritis or aids the healing of ligament and muscle tissues. *Conclusion* The rationale for the use of PRP to improve tissue healing is strong, but the efficacy for many musculoskeletal applications remains unproven. PRP has been shown to be a safe treatment. A number of questions regarding PRP remain unanswered, including the optimal concentration of platelets, what cell types should be present, the ideal frequency of application, or the optimal rehabilitation regimen for tissue repair and return to full function.

Keywords platelet-rich plasma · ligament · healing · osteoarthritis · tendon

Introduction

The impact of musculoskeletal pathologies is immense and the widespread clinical burden has encouraged the search for products that effectively augment healing. Biologic healing utilizes the normal mechanisms for tissue repair and incorporates these at the site of injury. Blood components such as platelets migrate to the injury site and play an important role in tissue repair. Platelets contain various growth factors and cytokines that initiate and promote healing by stimulating cell migration, cell proliferation, angiogenesis, and matrix synthesis. Platelet-rich plasma (PRP) has received increasing interest across many musculoskeletal disciplines and has been widely applied clinically to stimulate tissue healing in numerous anatomical regions. PRP is formed by isolating and concentrating platelets from peripheral blood and is the plasma fraction of autologous blood having a platelet concentration above baseline [39].

PRP was first used by Ferrari in 1987 in open heart surgery to minimize the use of blood transfusions [16]. The known actions of platelet-derived factors suggest that PRP may have significant potential in the treatment of pathological conditions of cartilage, tendon, ligament, and bone. The efficacy of this treatment modality remains unproven, and there is little and often inconclusive evidence to guide clinicians as to the value of this therapy.

Our aims in writing this review include defining what PRP is, what different preparation systems are used in current practice, and how PRP is proposed to function. We aim to address the following questions: (1) is PRP a safe and effective treatment for tendon injuries? (2) is there basic science support and clinical evidence that PRP can decrease

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pain and improve the function of patients with muscle and ligamentous injury? and (3) what basic science and clinical evidence exists regarding the effects of PRP regarding structural and functional repair of damaged cartilage in early osteoarthritis?

Methods for Identification of Relevant Literature

The search engines used for this review included PubMed Central and Google Scholar. Keywords used for the search were “platelet rich plasma” and/or “tendon,” “ligament,” “muscle,” “osteoarthritis,” and “therapy.” The searches revealed a large number of studies; PubMed had 2,100 citations and Google Scholar had 1,230,000 citations. As exclusion criteria were applied, 200 articles were identified in PubMed. We focused on all PRP clinical studies in humans related to tendon, muscle, ligament, and osteoarthritis. Basic science studies with control groups were also included. Eventually, 65 relevant and applicable articles were cited.

Results

PRP Mechanism of Action

The repair response to PRP application to an injury site has been described. A clot forms at the site of tissue trauma consisting of red blood cells (RBCs), white blood cells (WBCs), and platelets entrapped within a fibrin matrix. Platelets contain α -granules that are a rich source of proteins, cytokines, and other bioactive factors that initiate and regulate wound healing [19]. The normal platelet count is 150,000/ μ l to 400,000/ μ l. Uncertainty remains as to the critical platelet concentration that will correlate with a clinically important enhancement of healing. Data in the literature suggests that a platelet count of three to five times the baseline or at least 1,000,000/ μ l is clinically significant, although values ranging from 2 to 8.5 times have also been proposed [21, 45]. A greater than fivefold increase in platelet concentration has not been shown to further improve healing, as in vitro studies have demonstrated that the dose–response curves of most growth factors are not linear [19]. While a critical dose may exist, using too great a concentration can, in some models, have negative effects, such as a reduction of transforming growth factor beta (TGF- β)-induced collagen synthesis, platelet-derived growth factor (PDGF)-induced bone synthesis, or inhibition of cell function [36, 48].

Platelet life span is 5–9 days. The platelet α -granules act as a reservoir for these growth factors. Once activated, the α -granules in the platelets secrete their growth factors with an initial burst and then through their life span. Approximately 70% of the stored factors are secreted within the first 10 min following activation and within the first hour almost 100% have been secreted [39]. Depending on where they are in the course of their life, some platelets will die within a few days and others may last up to 9 days continuing to regenerate additional growth factors.

The degranulation of the α -granules results in the release of PDGF, TGF- β , insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF), with a host of other growth factors as well. These are native growth factors in their biologically determined ratios [39]. Other important bioactive factors released from platelets include histamine and serotonin. These platelet growth factors enhance DNA synthesis, chemotaxis, angiogenesis, increase collagen deposition, and stimulate synthesis of extracellular matrix [25]. Individually, they demonstrate different properties. In vitro, PDGF has been shown to stimulate type I collagen production and messenger RNA expression in osteoblast and chondrocytes [31]. In the rabbit medial collateral ligament (MCL) rupture model, the application of PDGF-BB delivered in a fibrin sealant improved the ultimate load and energy absorbed to failure compared to a control group [30]. PDGF can thus potentially enhance ligament and tendon healing.

IGF has anabolic effects on healing tendons by stimulating protein synthesis and increasing cell proliferation and collagen synthesis. IGF plays a critical role in enhancing muscle regeneration after injury by stimulating myoblast proliferation and differentiation [15]. IGF is also found in the original plasma [9]. During the regenerative phase, IGF stimulates muscle cells rather than myofibroblasts, thus inducing the formation of normal muscle rather than fibrotic scar tissue [28].

TGF- β has an important role in cell differentiation and extracellular matrix synthesis. It can stimulate differentiation of mesenchymal cells into cells with a chondrocyte phenotype and induces synthesis of type II collagen and proteoglycans by mesenchymal cells. These suggest a role of TGF- β in regulating chondrocyte differentiation and cartilage matrix production [33]. TGF- β upregulates tissue inhibitors of metalloproteinases in human and bovine articular cartilage. Since matrix metalloproteinases (MMP) may have a negative effect on cartilage due to matrix breakdown, upregulation of the inhibitors suggests that TGF may contribute to cartilage healing [20]. However, TGF- β also appears to encourage the formation of fibrosis following muscle injury by stimulating the production of extracellular matrix proteins and inhibiting their degradation [37]; thus, it may be less helpful for the restoration of normal muscle tissue.

VEGF has a potent angiogenic effect and is expressed in high concentration in healing flexor tendons 7–10 days following repair in animal models [64]. Increased vascularity may improve tendon healing and contribute positively to the repair process.

Currently Available PRP Preparations

There are several different commercially available PRP preparations, including platelet-rich concentrate, platelet gel, platelet releasate, autologous conditioned serum, and isolated growth factors [19]. The differences between these various products have not been well-described. These products have been used clinically since the early 1990s for wound healing and maxillofacial and spine applications

[19]. This review will primarily focus on pure PRP application to clinical practice, with the acknowledgement that there are few level I controlled clinical trials to date.

Multiple commercial products deliver different concentrations of the platelets, RBCs, and WBCs. The optimum concentration of PRP is unknown and likely varies for different tissue types. A recent study compared growth factor and platelet concentrations from three commercial systems: Cascade (MTF Sports Medicine, Edison, NJ, USA), Magellan (Arteriocyte Inc., Cleveland, OH, USA), and GPS III (Biomet Orthopaedics Inc., Warsaw, IN, USA) [7]. They were all shown to increase the platelet concentration compared to autologous blood by approximately two to eight times that seen in whole blood. There was, however, a significant difference in platelet capture efficiency between the different preparations, the highest being with Cascade and Magellan followed by GPS III. Clear differences have been demonstrated in the biological profiles of PRP between different preparation systems, thus PRP produced by different systems cannot be assumed to be a homogeneous product across the population. Varying biological profiles may exist between different patients or even within the same patient over different time points. There was also a significant difference in WBC concentration, with greater concentrations in the GPS III and Magellan than Cascade. This raises the question of whether WBCs are helpful or harmful in this PRP delivery system. Increased WBCs can enhance further tissue repair due to cytokines contained in WBCs, but they may also increase local inflammation and may, therefore, impede tissue recovery [7]. The effect of WBCs within a PRP preparation is likely to be tissue specific.

Leukocyte-rich PRP may enhance the antibacterial effect of PRP. However, neutrophils release MMPs which can lead to increased muscle damage after injury [3]. Some studies have supported the correlation between increasing leukocyte concentration in platelets and elevated levels of some inflammatory cytokines [3], all of which suggest injury and a possible negative effect of WBCs on healing. Furthermore, the concentration of WBCs in PRP has been shown to positively correlate with the expression of catabolic MMP-3 and MMP-13 in equine tendon explants [41]. RBC presence in the PRP matrix may have an irritant effect due to the heme in the RBCs; thus, fewer RBCs in the mix may allow less pain after injection.

Activation of platelets is mediated by the transmission of a number of intracellular signals which result in the secretion of biologically active proteins or second messengers such as ADP [1, 59]. Platelet activation and growth factor release occurs with the addition of calcium or thrombin or the exposure to collagen. In this way, the platelets can be activated with calcium or thrombin just prior to injection or once injected into the patient by activation with the patient's own collagen to then release the growth factors. There are, therefore, some time restraints when using PRP in order to avoid premature activation far in advance of injecting the patient. The choice of platelet activator will affect the growth factor release profile from platelets. Harrison et al. demonstrated that thrombin-

activated platelets released growth factors immediately, whereas collagen activation of PRP resulted in a slower sustained release over 5 days [29].

Once produced, the PRP is then administered to the abnormal area. The use of local anesthetic before or in conjunction with injection of the PRP is controversial. The anesthetic may change the pH of the tissue and decrease the effectiveness of the PRP [19]. Also, bupivacaine has been demonstrated to be cytotoxic to human chondrocytes [5, 24]. A preferred method may be spraying the site with ethyl chloride and avoiding infiltration with local anesthesia.

Connective tissue healing begins with an inflammatory cascade, followed by proliferation/regeneration and remodeling phases. The effect of PRP probably depends somewhat on the inflammatory healing cascade which can be inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) [57]. Therefore, current recommendations are to avoid NSAID use for 1 week before and 2 weeks after PRP injection, although this recommendation is somewhat arbitrary and further study is required.

Tendon Healing

Basic laboratory studies demonstrate that tendon healing proceeds through scar tissue formation, in a process that can take up to 1 to 2 years to mature. Infiltrating fibroblasts appear morphologically different than native tenocytes and the collagen is different than normal tendon [43]. When associated clinical symptoms of pain and dysfunction accompany this outcome, PRP may rebalance the "healing" equation and move towards the formation of type I collagen rather than type III collagen that has inferior strength properties. Normally, type I collagen accounts for 65–80% of tendon collagen [56].

Several recent studies have demonstrated the positive effects of PRP on gene expression and matrix synthesis in the tendon. Equine tendon explants cultured in PRP demonstrated increased gene expression of type I collagen, type III collagen, and cartilage oligomeric matrix protein without an increase in catabolic molecules MMP-3 and MMP-13 [55]. In another study, equine flexor digitorum tendons cultured in PRP produced higher concentrations of TGF- β and PDGF-BB compared to the effect of other blood products [40].

In the study of Majewski et al., accelerated healing of rat Achilles tendons has been reported in response to autologous condition serum. The autologous condition serum-treated tendons were thicker, produced more type I collagen, and had accelerated recovery of tendon stiffness [38]. Zhang et al. reported that PRP releasate in adult rabbits promoted the differentiation of tendon cells into active tenocytes that exhibited high proliferation rates and collagen production capabilities [65]. Human tenocytes cultured in PRP showed increased cell proliferation and total collagen production [10].

Chronic patellar tendinosis occurs most commonly at the proximal bone-tendon junction [19]. PRP was injected into healthy rat patellar tendons and concluded to be a safe and effective treatment. Histological analysis after injection

demonstrated increased levels of type I and type III collagen, consistent with tendon repair and remodeling [32]. It is possible that PRP therapy may have limited effects on normal tissue and may be more effective for treating diseased tendons. These basic laboratory studies suggest the potential for a positive clinical effect of PRP.

Clinical Studies

There are several reported randomized trials that compare PRP with various other injectates for the treatment of lateral epicondylitis. A case control study compared 15 patients with chronic epicondylar tendinosis who were treated with PRP to 5 patients treated with bupivacaine only. PRP led to far better relief of pain as measured by visual analog scale (VAS) at 4 weeks, 6 months, and 2 years [41].

One prospective randomized trial reported a positive effect of PRP treatment in lateral epicondylitis [44]. One hundred patients with chronic lateral epicondylitis were randomly assigned to PRP treatment ($N=51$) or corticosteroid injection ($N=49$). Both treatment groups achieved significant reduction in pain, but relief for the PRP group lasted greater than 6 months unlike the corticosteroid group. Five patients in the PRP group and 13 patients in the corticosteroid group suffered recurrent symptoms and were treated with either surgery or a second injection by 6 months. At 1 year, VAS ($p=0.001$) and DASH ($p=0.005$) scores for the PRP group were significantly better than the corticosteroid group, and the improvement in pain and function persisted at 2 years follow-up [23]. Our own study examined 114 patients who underwent ultrasound-guided PRP injections for chronic elbow epicondylitis. A significant reduction in baseline VAS pain scores was noted, as well as improved functional scores and sports activity levels at 6 and 12 months. Of the 27 patients who completed magnetic resonance imaging (MRI) scans at 1 year following PRP treatment, there was a significant improvement in tendinosis, but while some tears improved, it was not a significant change (Fig. 1).

The effects of PRP on rotator cuff healing have been investigated in a number of studies. A prospective case series of 14 patients treated with PRP reported a significant improvement in VAS, Constant, and UCLA scores at 2 years without adverse effects, although there were no controls [46]. The same group reported a randomized controlled double-blind study comparing 26 patients who received PRP during rotator cuff repairs to 27 controls without PRP [47]. During the first 30 days after treatment, the PRP group had significantly less pain during the first 30 days after treatment and improved clinical scores, range of movement, and strength at 3 months only. However, there was no difference in healing as measured by MRI. We have also evaluated platelet-rich fibrin matrix (PRFM) in rotator cuff tendon healing [49]. Seventy-nine patients were randomized to receive either PRFM ($N=40$) or no implant ($N=39$) during surgical repair. There were no differences in outcome between the two groups based on ultrasound imaging of repair site integrity, patient-reported outcomes using validated outcome scales, or manual muscle strength

Fig. 1. Coronal inversion recovery images of an elbow in a 57-year-old man treated with PRP injection. The preoperative MRI (a) demonstrates severe degeneration of the common extensor origin (thick black arrow) with a partial thickness intrasubstance tear (thin black arrow) and adjacent extracapsular soft tissue edema (short black arrow). On the follow-up MRI (b) performed 3 months after treatment with PRP, there is only mild tendinosis (white arrow) with resolution of the previously seen partial thickness tear

at 1 year. The effects of PRFM on rotator cuff healing of small and medium tears were evaluated in another randomized controlled trial [8]. After 16 months, there was no difference in the Constant score or on MRI appearance. A final, small randomized trial of 20 patients undergoing repairs for rotator cuff tears [66] compared PRP to direct repairs. No difference was found in the clinical or strength tests at 12 months. However, ultrasound Doppler studies indicated significantly higher blood flow in the PRP group at 6, 12, and 26 weeks postoperatively.

Additional studies have examined Achilles tendon healing following PRP injection [12]. PRP and saline injections for chronic Achilles tendinopathy were compared in a randomized controlled double-blind study. Three ultrasound-guided PRP or saline injections were delivered via different punctures and the rehabilitation included progressive eccentric exercises. At 6 months, there was no significant difference between the two groups. Another study by the same group found that ultrasound imaging did not demonstrate any significant change in the tendon structure or neovascularization [11]. The authors suggested that the lack of difference might have been due to the eccentric exercises, which is known to have a positive effect on blood flow.

PRP has also been used to augment Achilles tendon repairs. A randomized controlled single-blinded trial compared PRP after their Achilles repair to direct repairs only [54]. The re-rupture score was lower in the group treated with PRP, although no difference was detected in the tendon elastic modulus or the heel raise index. The PRP was stored overnight prior to surgery, which may have affected its biological profile. A small case series followed patients with Achilles tendinopathies who were treated with PRP [22]. By 18 months, the PRP-treated group reported a significant

improvement in functional outcomes, although there was no control group for comparison. A small retrospective case series compared Achilles repairs augmented with a “preparation rich in growth factors” (PRGF) to controls [51]. The mean follow-up was 32 months for the PRGF group, who had an improved range of motion and earlier return to activities, while ultrasound evaluation also revealed smaller-sized Achilles tendon tears.

A small case control series compared chronic patellar tendinopathy treated by PRP to untreated controls [17]. While the PRP group reported a greater improvement in sports activity, there was no difference in VAS, time to recovery, or patient satisfaction. A prospective case series of PRP treatment for chronic patellar tendinopathy reported that, at 6 months, 70% of patients reported marked or complete improvement and 80% of patients were satisfied; however, there was no control group for comparison [35]. Other tendons have also been treated with PRP, with limited published data. A small number of cases of chronic plantar fasciitis treated by PRP reported that six of the nine patients achieved complete symptomatic relief after 2 months. Similarly, this study did not have any controls [4].

Review of these animal and human studies suggests that PRP may play a role in the treatment of chronic tendinopathy. The 2010 International Olympic Committee consensus paper on the use of PRP in sports medicine concluded that PRP is a treatment option for chronic tendon injuries [14]. However, further study is required to identify the optimal PRP preparation, dosing protocol, and timing for various tendon disorders. The ideal post-injection physical therapy protocols for different anatomic areas also need to be determined.

Current protocols for use of PRP in tendinosis involve imaging to locate the point of maximum abnormality. A gradual post-injection physical therapy protocol is followed, which begins with range of motion, progresses to stretching, then eccentric exercises, and finally return to full activity by 8 weeks with return to sports when pain-free. For chronic midsubstance Achilles tendinopathy, following ultrasound-guided PRP injection, protecting with a brace for 2–4 weeks is recommended. Early range of motion is initiated, followed by gentle stretching and then progression to eccentric exercises. Gradual return to full activity occurs after 8 weeks.

Applicability of PRP Therapies to Muscle Injuries

Traditionally, muscle injuries are treated with ice, anti-inflammatory medication, and rehabilitation. NSAIDs may increase the expression of TGF- β and decrease prostaglandin E₂, and in this way, may favor fibrosis versus muscle regeneration [28]. PRP, with the introduction of growth factors in physiologic proportions, could possibly accelerate healing and shift the balance to a proliferative effect with more muscle cell regeneration.

Platelets are rich in growth factors that can stimulate myogenesis and mitigate inflammation. For example, it is known that PDGF and IGF stimulate myogenesis [26]. Hammond et al. examined the use of autologous PRP to

treat muscle strain injuries in a rat model. These authors studied two types of muscle injury in the rat anterior tibialis muscle. Group I was a single large strain contraction and group II was multiple small strain lengthening contractions. They observed that recovery of contractile function after injury by a single, large strain lengthening contraction involved repair of the damaged sarcolemma with minimal myogenesis. In contrast, recovery from multiple, small strain lengthening contractions required myogenesis, with minimal sarcolemma repair [27]. In group 1, the PRP somewhat improved stability of the muscle to generate force, but only on day 3; otherwise, recovery and time to full return of function was not altered. In group 2, the PRP resulted in a significant improvement at several time points as well as quicker return to full function. This effect was felt to be due to increased myogenesis [27].

PRP treatment for muscle injuries in humans has been reported to improve muscle healing [63]. Eighteen professional sportsmen with a variety of muscle strains were treated with autologous conditioned serum and reported faster healing by almost 1 week compared to a similar group of 11 professional sportsmen treated with Actovegin® (Nycomed, Zurich, Switzerland) [62]. This was a retrospective study with no untreated control patients. However, the 2010 International Olympic Committee consensus paper on the use of PRP in sports medicine concluded that there was little scientific support for the use of PRP in muscle strain injuries [14].

Consideration of the pathophysiology of muscle healing suggests that PRP should probably not be recommended in the first 24 h of injury. PRP may be most effective in the regenerative phase, a few days after injury, but the indications for PRP in muscle injury seem very limited at this time and further data are required.

Treatment of Ligament Injuries with PRP

The application of PRP for ligament repair is less well studied. In one study, various growth factors were applied to ruptured MCLs in a rabbit model using a fibrin sealant delivery system. Higher doses of PDGF-BB resulted in greater ultimate load and energy to failure, but adding TGF- β did not further increase structural properties [30].

PRP application in anterior cruciate ligament (ACL) allograft healing was evaluated in a level I double-blind randomized clinical trial [42]. No statistically significant differences were measured in inflammatory parameters, MRI appearance of the graft, or clinical outcome. In contrast, another level I study of PRP effects on ACL healing compared patients treated with PRP to those treated with a primary ACL repair only [60]. At 4–6 weeks, there was greater MRI evidence of revascularization at the osteoligamentous interface, although this improvement did not persist between 10 and 12 weeks. However, there was no assessment of clinical outcomes for the small sample groups. A small case control study compared outcomes from ACL reconstructions created with a PRGF to conventionally repaired ACLs [52]. At an average of 15 months from the index procedure, some patients

underwent a second-look arthroscopy and biopsy samples were taken. While no difference in arthroscopic appearance was noted, greater remodeling was noted in the PRGF group based on histology. Further data is necessary before PRP can be recommended for the treatment of acute ligament injury.

Is There a Place for PRP in Osteoarthritis?

Basic Laboratory Studies

It has been established that progressive chondrocyte death occurs after impact injury [58]. Chondrocyte death can occur even with low-impact energies that are insufficient to fracture the cartilage surface. Two important growth factors needed in cartilage repair are IGF and PDGF. IGF balances proteoglycan synthesis and breakdown. Incorporating IGF into a fibrin clot that was placed in equine cartilage defect improved the quality and quantity of repair tissue and reduced synovial inflammation [18]. Age also has an adverse effect on cartilage biology, with decreased responsiveness of chondrocytes to IGF-1. This IGF nonresponsiveness has been further observed in arthritic cartilage and in the presence of inflammation [18]. These findings suggest the need for a chondroprotective agent. It remains unclear as to whether PRP as an intervention potentially has a role in chondrocyte repair or protection.

Intra-articular PRP was evaluated in seven horses with severe degenerative joint disease [6]. The animals were given three injections at 3-week intervals with a follow-up at 1 year. Clinical improvement was noted at 2 months and persisted at 8 months with no adverse clinical affects. PRP has been reported to have a proliferative effect on both autologous chondrocytes and mesenchymal stem cells in an ovine model [13].

Synovial cells were isolated from 10 osteoarthritic patients, cultivated in a serum-free media, and then exposed to either a platelet poor preparation or PRGF for 72 h. The PRGF group had significantly enhanced hyaluronic acid secretion compared to the platelet-poor preparation [2].

Clinical Studies

The effects of PRP and hyaluronic acid injections have been compared in two case control studies. In one such study, 60 patients were treated with PRP and 60 were treated with hyaluronic acid. At 12 months, the PRP-treated group reported significantly reduced pain and recovered better articular function [50]. A similar study compared 30 patients with knee osteoarthritis who were treated with PRGF to 30 patients treated with hyaluronan injections. Evaluation at 5 weeks found success rates of 33.3% for PRGF and 10% for the hyaluronan group based on the WOMAC scale [53]. A limited number of published case series have investigated clinical outcomes following treatment of knee osteoarthritis with three PRP injections. A study of 312 patients with knee osteoarthritis (Outerbridge grades I–IV) reported a significant improvement in pain, stiffness, function, and the Lequesne Index and WOMAC

scale at 6 months [61]. Another case series followed 114 patients with degenerative articular lesions (58 Kellgren group 0, 32 Kellgren groups I–III, and 24 Kellgren group IV) who reported a significant improvement in all clinical scores at 12 months with maximum improvement at 6 months [34]. Fourteen patients with osteoarthritis had no significant difference in their ultrasound appearance or clinical outcomes at 6 months [50].

We are completing a case series of 22 patients with early knee osteoarthritis who were treated with Cascade™ PRP with 1 year follow-up. Inclusion criteria were Kellgren grades 0–II osteoarthritis, with knee pain for patients aged 30–70 years. Patients were evaluated using MRI (T2 relaxation time was assessed as a measure of collagen organization and T1 rho as a measure of proteoglycan content), VAS and WOMAC scales, and a functional step-up test. These evaluations were done prior to treatment and then repeated at follow-up at 1 week, 4 weeks, 2 months, 6 months, and 1 year. Our preliminary data on this very small sample suggests an improvement in the VAS pain at 6 months ($p < 0.001$) and 12 months ($p < 0.001$), as well as improved WOMAC functional score improvements at 6 months ($p = 0.005$) and at 12 months ($p = 0.010$). MRI evaluation was undertaken in 14 patients both prior to PRP treatment and at 1 year (Fig. 2). All patients had patellofemoral joint (PFJ) and medial compartment involvement, but only eight patients also had osteoarthritic changes involving the lateral compartment. No significant improvements were seen in the PFJ, lateral or medial compartments. However, only 1 of the 14 patients demonstrated progression of osteoarthritic changes on MRI.

Discussion

PRP is widely used for a number of musculoskeletal applications. The biologic rationale for the use of PRP to

Fig. 2. Coronal FSE knee images in a 65-year-old woman treated with intra-articular PRP injection. The baseline MRI (a) demonstrates high-grade partial thickness cartilage wear over the medial femoral condyle (thick black arrow) and medial tibial plateau (modified Outerbridge score 3). There are medial and lateral compartment osteophytes (thin black arrows). On the follow-up MRI (b) performed 1 year after PRP injection, the appearance of the cartilage is unchanged

improve connective tissue healing is strong. Uncertainty exists as to the clinical efficacy and appropriateness of PRP application to a number of musculoskeletal pathologies. This review explored the current evidence regarding the musculoskeletal applications of PRP to tendon, ligament, muscle, and early osteoarthritis. PRP has an excellent safety profile, and this has encouraged its application to numerous musculoskeletal complaints.

The promising in vitro effects of PRP for improving tendon, ligament, and muscle injuries have not predictably translated to improved outcomes following treatment with PRP in a number of clinical studies. The results from such studies have been variable and there is no clear trend or consensus regarding the effectiveness of PRP for clinical orthopedic applications. PRP treatment of injuries of the common extensor and flexor tendons associated with lateral and medial epicondylitis is associated with the most significant improvement in clinical trials. Other PRP applications to damaged tendons such as the Achilles or rotator cuff tendons have not shown a significant improvement to date. Further data are required to support the use of PRP in tendon, ligament, and muscle injuries, although some promising studies have been reported. In depth pre- and post-injection imaging is essential with MRI and/or ultrasound to document tissue healing and imaging is lacking in most studies. Early osteoarthritis pain and functional limitations can improve with PRP application but further investigation is necessary especially with MRI imaging. Even in the absence of structural or functional improvements, PRP is often associated with a reduced need for narcotics, better sleep, and reduced perception of pain. This apparent disparity in clinical outcomes is not fully understood.

There are few well-designed and adequately powered randomized control trials involving PRP. More level I clinical trials are needed to assess clinical, structural, and biomechanical outcomes. Future level I studies are necessary to confirm early evidence of tendon healing for patients with chronic tendinosis and/or partial tears. Weight-bearing tendons such as the patella and Achilles tendons may require different PRP regimes than the nonweight bearing tendons of the elbow and shoulder.

It is currently unknown if PRP can accelerate healing of acute muscle, ligament, or tendon injuries where the biologic milieu is different from more chronic degenerative tendinopathy or osteoarthritis. An important caveat to the interpretation of PRP data is that different studies have used varying PRP preparation systems; without quantification of the biology of PRP, it cannot be assumed to be a homogenous treatment product. A number of questions related to PRP remain unanswered, such as what is the optimal concentration of platelets in PRP, what are ideal PRP formulations, what cell types should be present, what is the ideal frequency of application, and what rehabilitation regime should be used to optimize tissue repair and return to full function.

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